REMARKS

Claims 1-13 are pending in this application.

Examiner Interview

Applicants wish to thank the Examiner for the helpful and courteous telephone interview conducted on August 4, 2009. The Examiner "Interview Summary" forms dated August 11, 2009 accurately memorialized the general discussions.

During the interview, the following four points were discussed.

First, the presently claimed invention is a method of selecting an appropriate MS2 fragment ion as a precursor ion beforehand without repeating trial and error. On the other hand, Takegawa does not disclose, teach, suggest or provide any reason for such a guideline as pre-selection of the precursor ion.

Next, Takegawa merely uses a dominant ion as the precursor. Even if a high correlation coefficient of 0.928 is obtained between isomers 210.2 and 210.3, Takegawa does not disclose, teach, suggest or provide any reason for selecting other fragment ions as the precursor.

Then, the Examiner asserted that Takegawa teaches the idea that when the precursor has small correlation coefficients among the fragment patterns, the isomers can be differentiated by the fragment patterns. However, as mentioned above, Takegawa does not select other ions except the dominant ion as the precursor.

Lastly, the Examiner asserted that the mutual similarity index is the same as the correlation coefficient. However, the mutual similarity index is obtained before the precursor ion is fragmented. In addition, the mutual similarity index can be calculated beforehand, and can

be stored in a database. Therefore, with the mutual similarity index it is possible to rapidly identify a sugar chain.

Claim Rejections - 35 USC § 103

Claims 1-7, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takegawa et al. (Rapid Communication in Mass Spectrometry, 2004, IDS) (Takegawa).

Claims 8, 9, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takegawa in view of Armentrout (Topics of Current Chemistry, 2003).

Applicants respectfully traverse all the outstanding rejections.

The presently claimed invention is a method of selecting an appropriate MS2 fragment ion as a precursor ion beforehand without repeating trial and error. On the other hand, Takegawa does not disclose, teach, suggest or provide any reason for such a guideline as the previous selection. Takegawa only discloses the selection of only the dominant ion as the precursor.

During the interview, the Examiner disagreed with Applicants' argument and cited Figure 3(f) of Takegawa. According to the Examiner, in Figure 3(f) of Takegawa 782m/z is the dominant ion. The Examiner noted that the selected precursor ion was 790 m/z, the non-dominant ion.

Applicants respectfully submit that this is not accurate. While Takegawa does not select the dominant ion as the precursor, the reason that Takegawa selects m/z 790 ion in Fig. 3(f) as the precursor is obvious from the caption of Fig. 6. That is, this selection is done to be consistent with Fig. l(f). Fig. l(f) is an MS2 spectrum of PA-oligosaccharide isomer 101.4. This spectrum is obtained by selecting an m/z 790 precursor ion which actually is an $[M+H+Na]^2$

ion(molecular-related ion). On the other hand, Fig. 5(c) is an MS3 spectrum of fucosylated PA-oligosaccharide isomer 111.4. This fucosylated PA-oligosaccharide isomer 111.4 has a structure that a fucose is linked to the PA-oligosaccharide isomer 101.4. TheMS3 spectrum of Fig. 5(c) is obtained by selecting m/z 790 precursor, which is an $[M\text{-}Fuc+H+Na]^{2}$ ion ("-Fuc" denotes the loss of fucose), from MS2 fragment ions. As shown in the caption of Fig. 6, Takegawa selects $[M\text{-}Fuc+H+Na]^{2}$ ion as a precursor to match its MS3 spectrum with MS2 spectrum of the $[M+H+Na]^{2}$ ion. Therefore, it is meaningless to discuss whether the precursor ion is dominant or non-dominant. Takegawa does not disclose, teach, suggest or provide any reason for selecting other fragment ions as the precursor ion, as recited in the presently claimed invention.

Takegawa discloses the following point in his paper. In the MS3 spectral matching of the fucosylated PA-oligosaccharide, the MS3 spectrum obtained by selecting the defucosylated ion as the precursor is almost the same as the MS2 spectrum of the corresponding non-fucosylated PA-oligosaccharide. Therefore, it is useful for the MS3 spectral matching of the fucosylated PA-oligosaccharides if the MS2 spectra of the corresponding non-fucosylated PA-oligosaccharides are stored in a database. This is described on page 390, last paragraph of Takegawa. Takegawa refers to "based on Bn- and Yn-type fragmentations of the corresponding $[M+H+Na]^{2+}$ ions". See Takegawa, page 390. However, the data of Bn-type ion is not described in this paper.

By the collision-induced dissociation, various fragment ions are produced. Takegawa discloses the method of identifying the sugar chain structure by measuring the MS3 spectrum of the defucosylated ion. However, the fucose is linked not only to the reducing end of GlcNAc but also to the non-reducing end of Gal or GlcNAc. The variety of the sugar chain structures is

producing by the linking of fucose and/or sialic acid, sequences, branching, and anomeric structures as Takegawa also describes. There is not a little isomer which cannot be distinguished by only MS2 spectrum matching. See Takegawa, page 388, right column, lines 2-3. In this case, Takegawa describes that such an isomer can be identified by excluding the defucosylated ion of m/z 790 from the calculation of the correlation coefficient. See Takegawa, page 388, right column, lines 8-13. This reason is because the fucose has low binding (linking) energy and is easily released by the collision-induced dissociation. This operation can be performed if it is known beforehand that fucose is linked to the sugar chain. On the other hand, the presently claimed invention discloses the method of selecting a reasonable MS3 precursor ion for identifying the sugar chain structure without prior information about the sugar chain. Such an novel idea is not described, taught, suggested or provided a reason for in Takegawa.

Various signals are produced by the collision-induced dissociation in an MS2 fragmentation. Each signal of this fragmentation commonly includes plural kinds of fragment ions. See next section below for further comments on the fragmentation of Takegawa. However, Takegawa considers only the case where the structure of the precursor ion can be specified. It is impossible to specify the precursor ion unless the information about the sugar chain structure is obtained beforehand.

The Examiner asserts that, since Takegawa discloses that the fragment pattern can be differentiated when the correlation coefficient is low, this idea can easily apply to the selection of the precursor of the MS3 fragment pattern. However, Takegawa discloses that the sugar chain structure can be identified by using a correlation coefficient only when the structure of precursor

ion can be specified. Therefore, it is not obvious for one of ordinary skill in the art to develop a method of selecting the reasonable precursor ion from Takegawa's description when each signal of an MSn fragment pattern comprises various fragment ions in various ratios. For at least the reasons provided in the above explanation, Takegawa fails to render the presently claimed invention obvious.

During the interview, the Examiner asserted that since Takegawa discloses the selection of one MS2 fragment ion, it would have been obvious to select two or three fragment ions. Applicants respectfully disagree with this assertion.

Takegawa discloses that the sugar chain structure can be identified by using a correlation coefficient only when the structure of precursor ion can be specified, as discussed above. Therefore, the method of Takegawa does not disclose, teach, suggest or provide any reason for selecting two or three fragment ions.

Furthermore, the disclosure of Takegawa is merely limited to the fragmentation of MS1 to MS2, whereas Applicants' claimed method is the fragmentation of MS2 to MS3. It would not be obvious to one of ordinary skill in the art to apply the disclosure of Takegawa to another level of fragmentation, i.e., further fragmentation of MS2 to an MS3 fragmentation pattern.

Therefore, Takegawa discloses only a case where the structure of the precursor can be specified. As a matter of course, the structure of the precursor is limited to 1 in the fragmentation of MS1 to MS2. However, in the fragmentation of MS2 to MS3, the structure of the precursor is not limited to 1. Many signals of the MS2 spectrum comprise the mixture of the

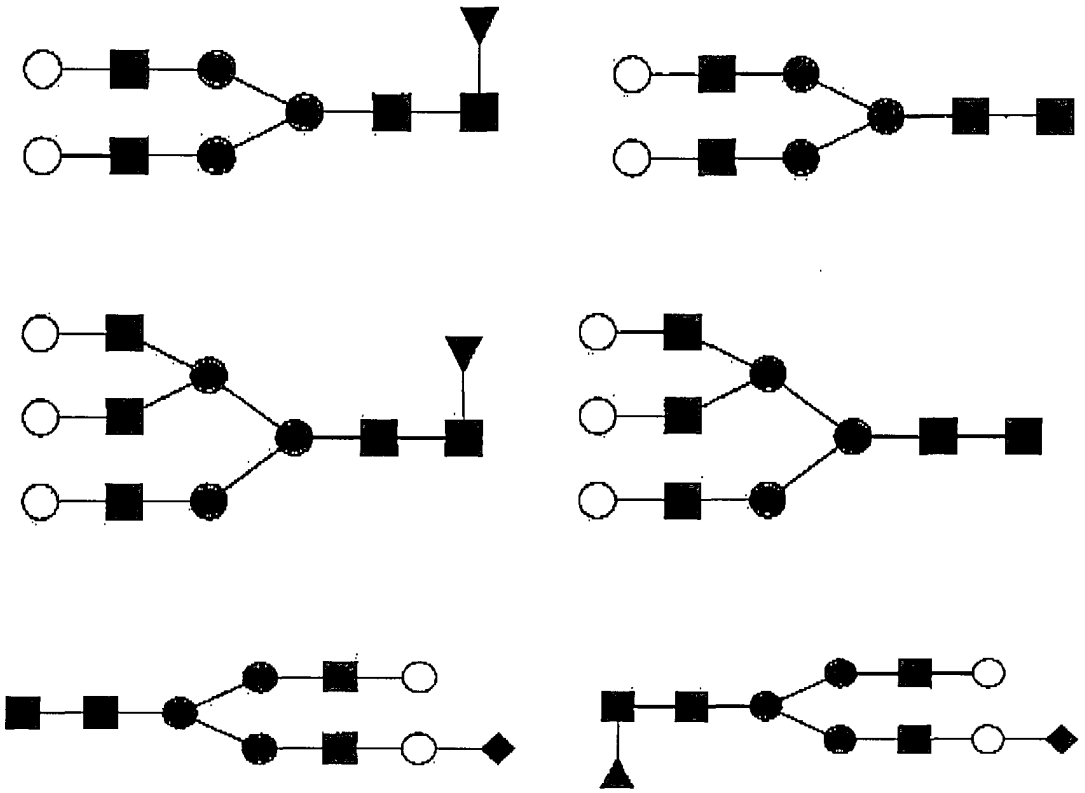
MS2 fragment ions. Takegawa's method cannot be used where the structure of the precursor is not limited to 1.

On the other hand, the presently claimed invention discloses a method of selecting the reasonable precursor ion for identifying the structure regardless of whether the signal comprises a mixture of structures or a single structure. Therefore, a skilled artisan would not consider the presently claimed invention obvious from the disclosure of Takegawa.

Fragmentation Method of Takegawa

Takegawa discloses the analysis of N-linked sugar chain structures in the cited reference. The N-linked sugar chain structures can be roughly classified into two types. The first type is the structure with α1-6 fucose connected to a GlcNAc residue at its reducing end. This fucose connected to the GlcNAc residue at its reducing end is called "core-fucose", and this type is called "core-fucose binding type". The second type is the structure wherein the fucose is not connected to the core (GlcNAc). This type is called "core-fucose non-binding type".

The following figure discloses each of the two types of N-linked sugar chain structures.

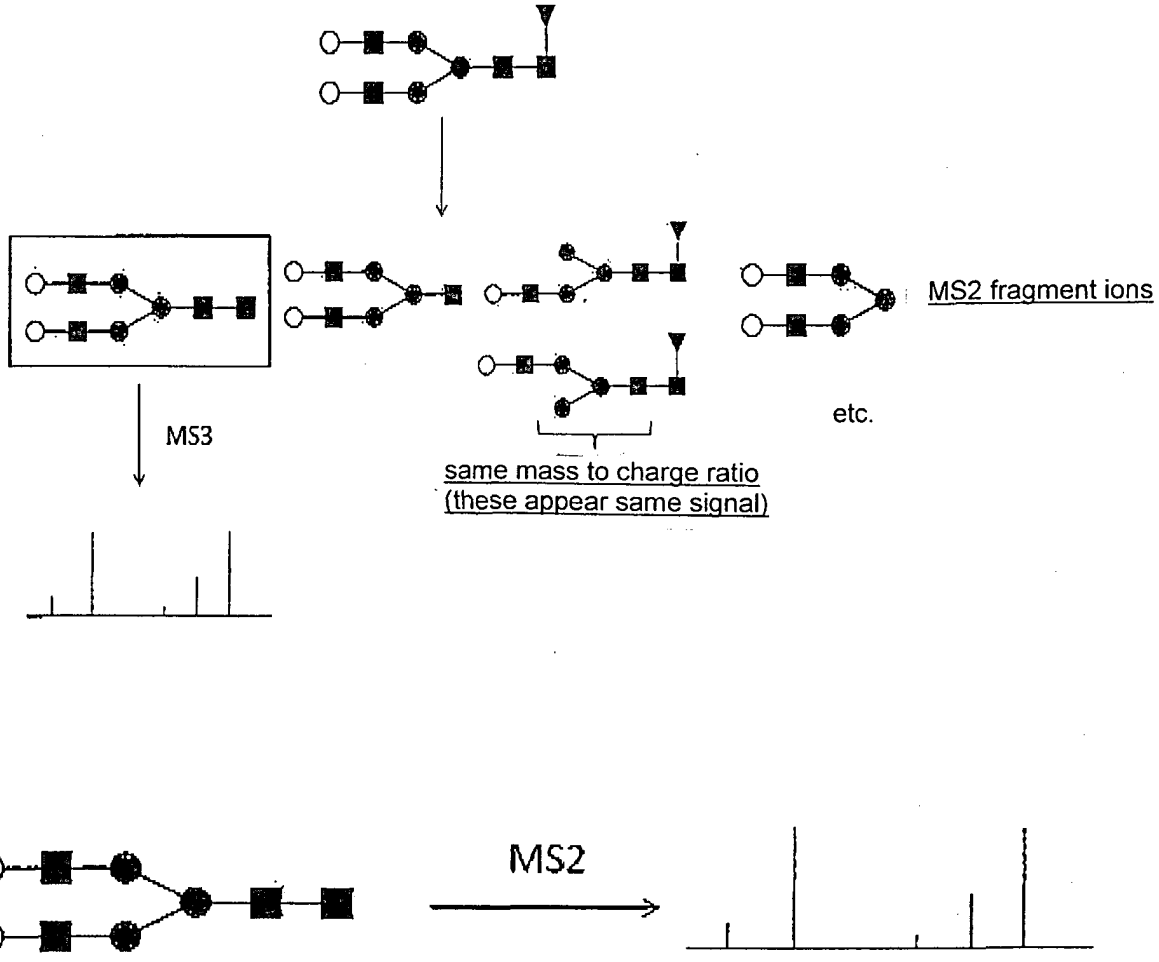


Left column : Core-fucose (the ▲) binding type
Right column : Core-fucose non-binding type

As shown in the above figures, the N-linked type is structurally restricted. If the N-linked sugar chain structures are the sugar chain structures of a Homo-sapiens, then these are classified to a structure with the fucose (core-fucose) and structure without the fucose. These two types have a variation in the side of the non-reducing end (the left side of branch). In the side of the reducing end (the right side of branch), the structure is restricted.

Takegawa discloses the following point in the cited reference. In the structure analysis of the core-fucose binding type, if an [M-Fuc] fragment ion(defucosylated ion) is selected as a precursor from MS2 fragment ions, and MS3 spectrum is measured, then this MS3 spectrum is

almost the same as a MS2 spectrum of the corresponding core-fucose non-binding type sugar chain structure. Therefore , it is useful for the structure analysis of core-fucose binding type if the MSn data of core-fucose non-binding type structure are stored in database.



Since the fucose has low binding energy, and is preferentially released by the fragmentation of an MS analyzer, dissociation of the fucose bond is often observed as a large signal in the MS2 spectrum. Only if the analyst knows beforehand that an analyzed sugar chain

structure is the core-fucose binding type and that the fucose is not linked elsewhere, then Takegawa's method can identify the structure by selecting the [M-Fuc] ion as the precursor. Otherwise, each signal of the MS2 fragment pattern is obtained as a mixture of many fragment ions as shown in the second from the right of the above figure. In this case, Takegawa's method cannot identify the sugar chain structure.

Conclusion

Takegawa discloses that a sugar chain structure can be identified by using a correlation coefficient only when a structure of precursor ion is limited to 1. The method of selecting the precursor ion for identifying the sugar chain structure is not described, taught, suggested or provided for at all within the disclosure of Takegawa.

Each signal of the MS2 spectrum comprises a mixture of many fragment ions having various structures in various ratios. In this case, Takegawa's method cannot identify the structure . Therefore, from the disclosure of Takegawa, it is not obvious for a skilled artisan to develop the method of the presently claimed invention, which selects the reasonable precursor ion which should be fragmented.

In order to specify the structure of precursor ion to 1, it is necessary to obtain beforehand the information of the sugar chain structure which is to be the target of analysis. If the sugar chain structure is completely unknown, then there is no guarantee that it is not a signal comprising the mixture of plural fragment ions, even if the ion of $[M\text{-}Fuc]^+$ or $[M\text{-}Neu]^+$ is selected as the precursor. Therefore, it is practically impossible to apply Takegawa's method to a completely unknown structure. On the other hand, the presently claimed invention discloses

the method to select the precursor ion which is useful for the structure identification regardless of whether the selected MSn signal comprises the single structure or a mixture of structures. This feature can be considered an inventive step of the presently claimed invention.

The selection of the reasonable precursor ion is useful for saving the amount of sample used, the measurement time, and the cost when the structure identification is performed. These are obvious advantages over the method of Takegawa.

In view of the above, Applicants respectfully submit that their claimed invention is allowable and ask that the rejections under 35 U.S.C. §102 and the rejection under 35 U.S.C. §103 be reconsidered and withdrawn. Applicants respectfully submit that this case is in condition for allowance and allowance is respectfully solicited.

If any points remain at issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the local exchange number listed below.

If this paper is not timely filed, Applicants respectfully petition for an appropriate extension of time. The fees for such an extension or any other fees that may be due with respect to this paper may be charged to Deposit Account No. 50-2866.

Respectfully submitted,

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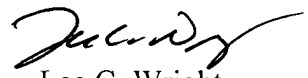

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